

**WHAT IS CLAIMED IS:**

1. A method of regulating bone formation in an individual, comprising the step of:

5 (a) administering a composition that alters the binding activity of Smad6 protein in said individual, wherein an increase in Smad6 protein results in an increase in Smad6/Hoxc-8 complexes which maintains transcriptional repression of genes involved in bone formation, wherein a decrease in Smad6 protein binding  
10 activity results in a decrease in Smad6/Hoxc-8 complexes, which relieves transcriptional repression of genes involved in bone formation, thereby regulating bone formation in said individual.

15 2. The method of claim 1, wherein said composition is selected from the group consisting of a transgene encoding Smad6, an antisense molecule directed towards Smad6, an antibody directed towards Smad6 and Hox proteins.

3. The method of claim 1, wherein said genes involved in bone formation are selected from the group consisting of osteopontin, osteoprotegrin, OPGL and RANK.

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4. A method of regulating nuclear bone morphogenetic protein signaling in an animal, comprising the step of:

(a) administering a composition that alters the binding activity of available Smad6 protein in a cell in said individual, wherein an increase in available Smad6 protein results in an increase in Smad6/Hoxc-8 complexes which maintains transcriptional repression of genes involved in bone formation, wherein a decrease in said available Smad6 protein binding activity results in a decrease in Smad6/Hoxc-8 complexes which relieves transcriptional repression of genes involved in bone formation, thereby regulating nuclear BMP signaling.

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5. The method of claim 4, wherein said composition is selected from the group consisting of a gene encoding Smad6, an

antisense molecule directed towards Smad6, an antibody directed towards Smad6 and Hox proteins.

5                    6. The method of claim 4, wherein said genes involved in bone formation are selected from the group consisting of osteopontin, osteoprotegrin, OPGL and RANK.

10                   7. A method of screening for a compound that disrupts transcriptional repression of a gene, comprising the steps of:

(a) combining Smad6 proteins and Hoxc-8 proteins in the presence and absence of a compound; and

15                   (b) detecting complex formation between said Smad6 proteins and said Hoxc-8 proteins, wherein a lack of complex formation between said Smad6 proteins and said Hoxc-8 proteins in the presence of said compound is indicative of a compound that disrupts transcriptional repression of a gene.

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8. The method of claim 7, wherein said detection of Smad6/Hoxc-8 protein complex formation is by means selected from the group consisting of a gel shift assay and a reporter transfection assay.

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9. A method of screening for a compound that disrupts transcriptional repression of a gene, comprising the steps of:

10 (a) combining a Smad6/Hoxc-8 complex and a DNA molecule in the presence and absence of a compound, wherein said DNA molecule comprises a Hox DNA binding element; and

15 (b) determining the amount of binding by said Smad6/Hoxc-8 protein complex to said DNA molecule, wherein less binding in the presence of said compound than in the absence of said compound is indicative of a compound that disrupts transcriptional repression of said gene.

20 10. The method of claim 9, wherein said DNA binding by said Smad6/Hoxc-8 protein complex is determined by means

selected from the group consisting of a gel-shift assay, a competitive binding assay, pull-down assay and immunoprecipitation assay.

5            11. A method of screening for a compound that disrupts transcriptional repression of a gene, comprising the steps of:

             (a) combining a Smad6/Hoxc-8 protein complex with a gene in the presence and absence of a compound, wherein said gene  
10 comprises a Hox DNA binding element; and

             (b) assaying for transcription of said gene, wherein an increase in the level of transcription in the presence of said compound relative to the level of transcription in the absence of said compound is indicative of a compound that disrupts  
15 transcriptional repression of said gene.

             12. The method of claim 11, wherein said transcription is assayed by means selected from the group consisting of a  
20 Northern blot, a Western blot, an enzymatic assay and a chemiluminescent assay.

13. The method of claim 11, wherein said gene is a reporter gene.

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14. The method of claim 13, wherein said reporter gene is selected from the group consisting of  $\beta$ -galactosidase, luciferase, secreted alkaline phosphatase and CAT assay.

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15. A method of regulating expression of gene that binds Hoxc-8, wherein binding by Hoxc-8 results in transcriptional repression of said gene, comprising the step of:

altering the amount of Smad6 protein, wherein an  
15 increase in said Smad6 protein binding activity results in an increase in Smad6/Hoxc-8 protein complexes, wherein an increase in said Smad6/Hoxc-8 protein complexes maintains said transcriptional repression of said gene, wherein a decrease in said Smad6 protein binding activity results in a decrease in Smad6/Hoxc-8 protein  
20 complexes, wherein a decrease in Smad6/Hoxc-8 protein complexes

relieves said transcriptional repression of said gene, thereby regulating expression of said gene.

5           16. The method of claim 15, wherein said gene is selected from the group consisting of osteopontin, osteoprotegrin, OPGLand RANK.

10           17. The method of claim 15, wherein said Smad6 protein is increased by means selected from the group consisting of overexpression of a Smad6 gene and upregulation of a Smad6 gene.

15           18. The method of claim 15, wherein said Smad6 protein is decreased by means selected from the group consisting of antisense hybridization to Smad6 RNA, antibody binding to a Smad6 protein and mutagenesis of a gene encoding Smad6.

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19. The method of claim 15, further comprising the step of:

increasing the amount of Smad1 protein, wherein said Smad1 protein binds said Hoxc-8, thereby relieving said  
5 transcriptional repression of said gene.

20. A method of inducing transcription of a gene encoding osteopontin, osteoprotegrin, OPGL or RANK comprising the  
10 steps of:

inhibiting Smad6, wherein in the presence of Smad1, said inhibition of Smad6 removes transcriptional repression of a gene encoding osteopontin, thereby inducing transcription of said gene.